

# Left Atrial Appendage Closure With the Watchman Device

A review of trial results and clinical application.

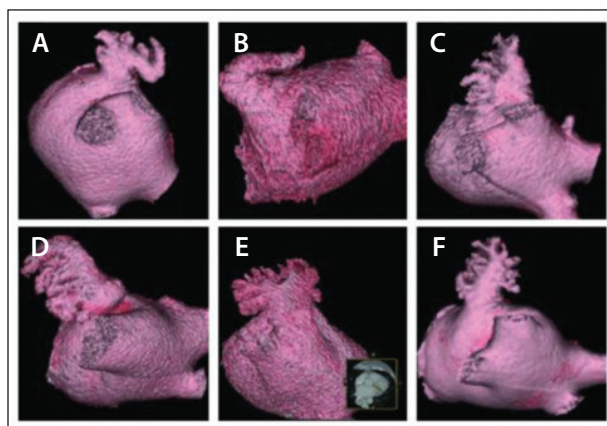
BY JAYANT KHITHA, MD, AND TANVIR K. BAJWA, MD

**A**trial fibrillation (AF) is the most common arrhythmia in clinical practice, with 3 to 4 million people in the United States having been diagnosed. AF accounts for approximately one-third of admissions resulting from cardiac rhythm disturbances.<sup>1</sup> Its prevalence averages from 1% to 1.5%, and its incidence increases with age to a rate of 19.2 per 1,000 patient-years in individuals aged 65 years or older.<sup>2</sup> Based on the ATRIA (Anticoagulation and Risk Factor in Atrial Fibrillation) study, the prevalence of AF is expected to increase 2.5-fold by 2050.<sup>1</sup> AF carries a significant risk of morbidity and mortality resulting from stroke, heart failure, and impairment of quality of life. Overall, AF-related in-hospital mortality is 1%, and in-hospital mortality is 1.9% for patients aged 80 years and older.<sup>3</sup> Patients presenting with AF have a fivefold increased risk of stroke.<sup>3</sup> Strokes secondary to AF have a worse prognosis than in patients without AF.<sup>2,4,5</sup> Moreover, 15% of patients with AF are known to have silent cerebral infarctions, confirmed by CT, as suggested by the SPINAF (Stroke Prevention in Nonrheumatic Atrial Fibrillation) data.<sup>6</sup>

The primary goal in treating AF is stroke prevention by means of oral anticoagulants (OACs) or by left atrial appendage (LAA) exclusion pursued surgically or percutaneously using implantable devices.

Warfarin is very effective in reducing morbidity and mortality in patients with AF, with a 64% reduction in stroke. However, it has been associated with an absolute risk increase in intracerebral hemorrhage and major bleeding of at least 2% to 4% per year, a narrow therapeutic window, and multiple drug interactions.<sup>7</sup>

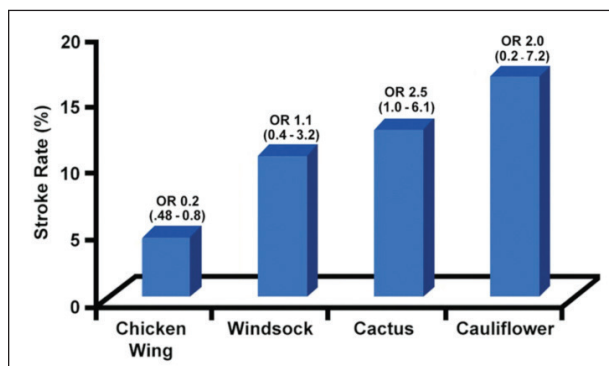
Approximately 30% of patients presenting with AF have a relative or absolute contraindication to the use of OACs.<sup>8-12</sup> Also, warfarin is associated with a high noncompliance rate of 20% over 2.5 years, according to the FRACTAL



**Figure 1.** General morphology classification of the LAA and the shape of LAA orifice are shown. LAAs are classified into four types, including chicken wing (A, B), windsock (C, D), cauliflower (E), and cactus (F). Figure adapted for reuse with permission from Wiley, from Wang Y, et al. Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. *J Cardiovasc Electrophys.* 2010;21:973–982.

(Fibrillation Registry Assessing Costs, Therapies, Adverse events and Lifestyle) data.<sup>13</sup> Moreover, only 50% to 68% of patients are in the therapeutic range when monitored, exposing them to an increased risk of stroke.<sup>14</sup> A large number of patients with AF are elderly and frail and have a significant bleeding risk (HAS-BLED score  $\geq 3$ , angiodysplasia, chronic renal failure, and cerebral amyloid angiopathy).

Novel OACs such as dabigatran, apixaban, edoxaban, and rivaroxaban have been shown to be noninferior or superior to warfarin but are also associated with increased bleeding risk and cost.<sup>15-17</sup> LAA closure offers an alternative treatment option for patients with AF for the prevention of stroke without increasing the risk of bleeding.



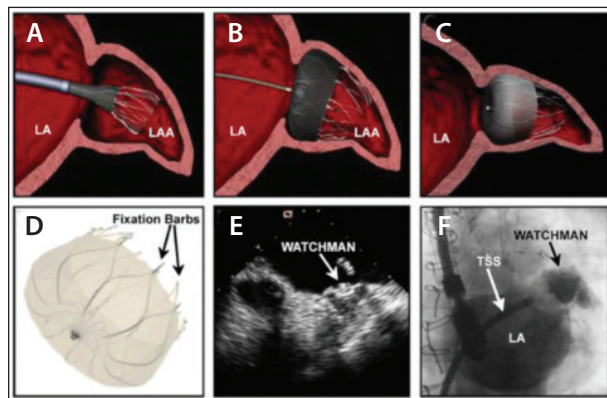
**Figure 2.** Prevalence of previous stroke/transient ischemic attack according to different LAA morphologies. Vertical bars represent the previous stroke/transient ischemic attack event rate with the univariate odds ratio (95% confidence interval) shown on top of the bars. Reprinted from *J Am Coll Cardiol*, vol. 60, Di Biase L, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study, 531–538, 2012, with permission from Elsevier.

### LAA ANATOMY AND MORPHOLOGY

The rationale for closing the LAA for stroke prevention is based on the fact that 90% of atrial thrombi in patients with nonvalvular AF (NVAf) are found in the LAA.<sup>7</sup> Other sources of thromboembolism include patent foramen ovale, atherosclerotic plaque of the thoracic aorta and carotid arteries, and left ventricular thrombus in patients with left ventricular systolic dysfunction.

The LAA is a 2- to 4-cm tubular structure attached to the left atrium. The lack of contraction in a fibrillating atrium leads to atrial stretch and dilation, promoting stasis and thrombus formation. Furthermore, AF is associated with endothelial dysfunction and impairment in the acetylcholine-mediated blood flow, which results in increased oxidative stress and promotes inflammation. This potentiates a prothrombotic state and increases the risk of thrombus formation.

The anatomy of the LAA is variable but important to evaluate prior to device implantation because it influences device selection and procedural success. Because the LAA occluder device is designed to cover the ostium and anchor in the neck, complete evaluation of the LAA with transesophageal echocardiography and a CT scan is recommended to define the morphology of the ostium, the width of the landing zone, and the length and shape of the LAA.<sup>7</sup> The LAA is classified into four group types based on morphology<sup>7</sup> (Figure 1): (1) chicken wing, which predefines the proximal bend of the dominant lobe; (2) windsock, which has a main lobe > 4 cm; (3) cauliflower, which is < 4 cm and does not have any forked lobes; and (4) cactus, which has



**Figure 3.** The top three panels illustrate the delivery (A), deployment (B), and release (C) of a Watchman LAA closure device through a transseptal delivery system. Panel D shows a close-up view of the Watchman device consisting of a self-expanding nitinol frame structure with fixation barbs designed to engage the LAA wall. Panel E shows a transesophageal echocardiography image of an occluded LAA after deployment of a Watchman LAA device (white arrow). Panel F shows a cine image of angiography in the left atrium demonstrating a Watchman device properly deployed inside the LAA (black arrow). Abbreviation: TSS, transseptal sheath. With kind permission from Springer Science and Business Media: *Curr Treat Options Cardiovasc Med.*, Vol. 14, 2012, pp. 503–519, Left atrial appendage occlusion and ligation devices: What is available, how to implement them, and how to manage and avoid complications, Aryana A.

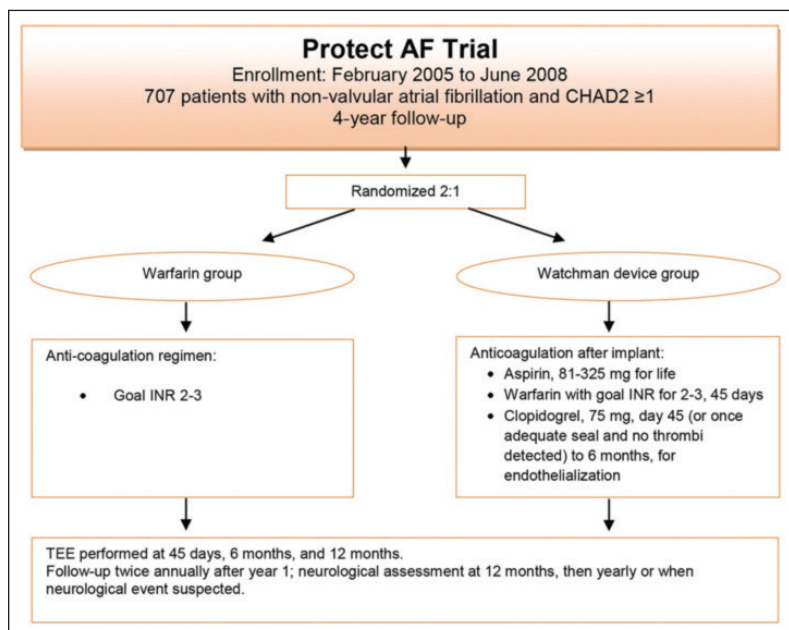
a main lobe and several daughter lobes. The chicken wing type is associated with the lowest risk of stroke among these morphologies, whereas the cauliflower type has the highest risk (Figure 2).

The ostium and neck of the LAA are also classified based on morphology as follows: horn-shaped (the ostium is wider than the neck), parallel tube (the ostium and neck are of similar dimensions), and angel wing (the neck has a longer dimension than the ostium). The horn-shaped morphology is associated with the highest rate of device embolization.

### WATCHMAN DEVICE

The Watchman device (Boston Scientific Corporation) is the only LAA occlusion device that has been approved by the US Food and Drug Administration (FDA). The device has a self-expanding nitinol frame with fixation barbs and a permeable polyester fabric cover and is available in sizes of 21, 24, 27, 30, and 33 mm. It is recommended that a device that is 10% to 20% larger than the LAA be used.<sup>7</sup>

Percutaneous LAA occlusion using the Watchman device is performed under transesophageal echocardiography and fluoroscopic guidance. Antibiotic prophylaxis is recom-



**Figure 4.** The PROTECT AF trial randomized patients to warfarin or LAA closure to examine the efficacy and safety of the Watchman device.

mended prior to the procedure. Vascular access is achieved via the femoral vein, and transseptal puncture is performed using the standard transseptal needle and sheath (Figure 3).

For better alignment with the axis of the LAA, the puncture site is preferred to be inferior and posterior. Once access is achieved, a pigtail catheter is advanced into the LAA, and angiography is performed in the right anterior oblique 30°/cranial 30° to confirm the morphology of the ostium, neck, and the LAA dimensions for appropriate device sizing. Heparin is generally administered to maintain an activated coagulation time > 250 seconds. Once anatomy is defined, the sheath should be advanced over the pigtail to reduce the probability of LAA perforation. The preloaded delivery catheter is then advanced to the tip of the access sheath, and the device is deployed by retracting the sheath.

## PROTECT AF TRIAL

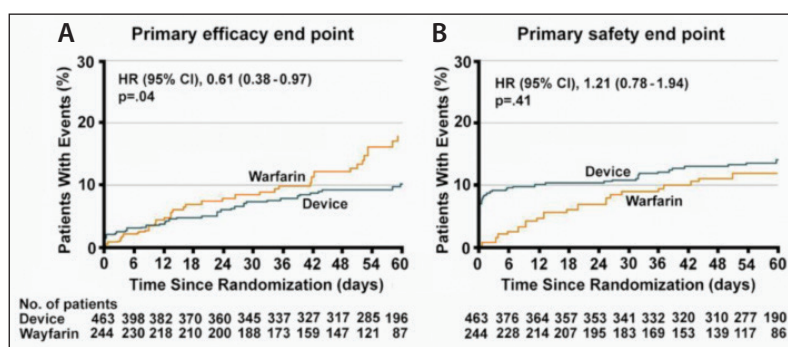
The PROTECT AF trial was a randomized, unblinded, multicenter trial conducted at 59 hospitals and involving 707 patients who were 18 years of age or older with NVAF, had one or more CHADS<sub>2</sub> risk factors (ie, age > 75 years, hypertension, diabetes, heart failure or left ventricular systolic dysfunction, previous transient

ischemic attack or stroke), and were eligible for long-term anticoagulation with warfarin (Figure 4).<sup>18</sup> Exclusion criteria included the presence of patent foramen ovale with atrial septal aneurysm, atrial septal defect, mechanical valve prosthesis, left ventricular ejection fraction < 30%, mobile atheroma of the aorta, and symptomatic carotid disease.

Overall, long-term follow-up data from the PROTECT AF trial revealed that patients with NVAF and at least one risk factor for stroke had a relative risk (RR) reduction of 40% (1.5% absolute reduction) in the primary composite efficacy endpoint of stroke, systemic embolization (SE), and cardiovascular/unexplained death after LAA closure as compared to warfarin (Figures 5 and 6).

There were 39 events among 463 patients (8.4%) in the device group (primary event rate, 2.3 per 100 patient-years) versus 34 events among 244 patients

(13.9%) in the warfarin group (primary event rate, 3.8 per 100 patient-years; RR, 0.6 favoring the device; 95% credible interval, 0.41–1.05), suggesting that the Watchman device met the criteria for noninferiority (posterior probability > 99%) and superiority (posterior probability, 96%). Cardiovascular mortality was lower in the device group than the warfarin group (1 vs 2.4 events per 100 patient-years; hazard ratio [HR], 0.4; 95% confidence interval, 0.21–0.75;



**Figure 5.** Kaplan-Meier curves for the primary efficacy and safety endpoints. The primary efficacy outcome was stroke, systemic embolization, or cardiovascular death (A). The primary safety outcome was a composite of major bleeding events and procedure-related complications (B). Incident probabilities for the intention-to-treat analysis are shown. Abbreviations: CI, confidence interval; HR, hazard ratio. Reprinted with permission from Vivek R, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312:1988–1998. Copyright © 2014 American Medical Association. All rights reserved.

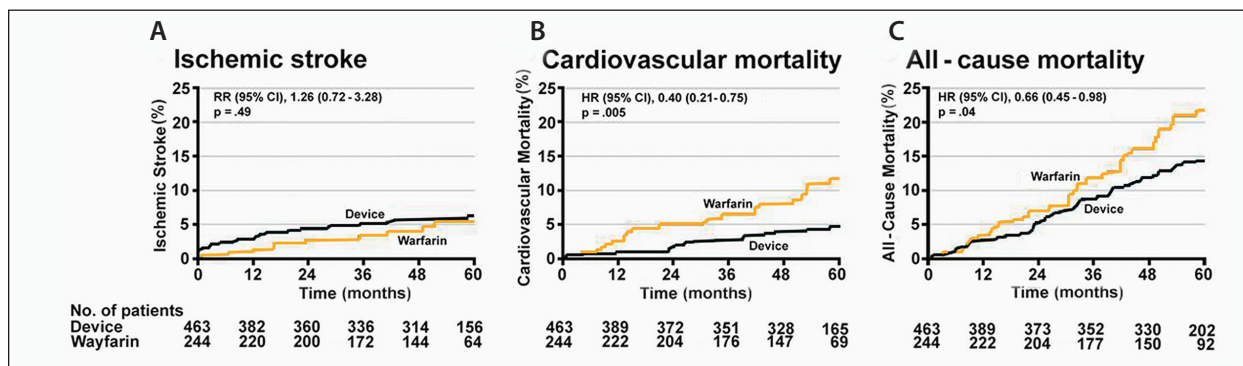


Figure 6. Kaplan-Meier curves for ischemic stroke, cardiovascular mortality, and all-cause mortality. Abbreviations: HR, hazard ratio; RR, rate ratio. Reprinted with permission from Vivek R, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014;312:1988–1998. Copyright © 2014 American Medical Association. All rights reserved.

$P = .005$ ). All-cause mortality was lower in the device group than the warfarin group (3.2 vs 4.8 events per 100 patient-years; HR, 0.66; 95% confidence interval, 0.45–0.98;  $P = .04$ ).

The primary safety endpoint was similar in both groups: 3.6 events per 100 patient-years (device group) versus 3.1 events per 100 patient-years (warfarin) (RR, 1.17; 95% credible interval, 0.78–1.95). The most frequent adverse events were pericardial effusion, device embolization, and stroke during the periprocedural period in the device group and major bleeding in the warfarin group. Noninferiority was achieved. Analyses were based on the Bayesian Poisson model and intention-to-treat analysis.

## PREVAIL TRIAL

A second trial was conducted to address concerns raised by the FDA about patient selection and early safety events in the PROTECT AF trial. The PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy) trial<sup>19</sup> was a randomized trial that further assessed the safety and efficacy of the Watchman device in patients with NVAF (Figure 7). Two coprimary efficacy endpoints and one safety coprimary endpoint were assessed. Of the randomized patients, 38.8% were from institutions that were not part of the PROTECT AF trial; 39.1% of procedures were performed by new operators (265 total procedures; 95% of attempted procedures resulted in successful implantation). The protocol for the antiplatelet regimens, transesophageal

echocardiography, follow-up, and neurology were similar to PROTECT AF.

The rate of the first coprimary efficacy endpoint (composite of stroke, SE, and cardiovascular/unexplained death) was similar in the device group as compared with the control group (0.064 vs 0.063, respectively), with an 18-month mean RR of 1.07 (95% credible interval, 0.57–1.89) and an upper bound margin of 1.89, which was higher than the predefined margin of 1.75. Hence, noninferiority was not achieved. This finding was attributed to the smaller sample size and the significantly lower number of adverse events of stroke or SE, particularly in the control group, compared to findings of contemporary trials of stroke prevention in AF (Figure 8).

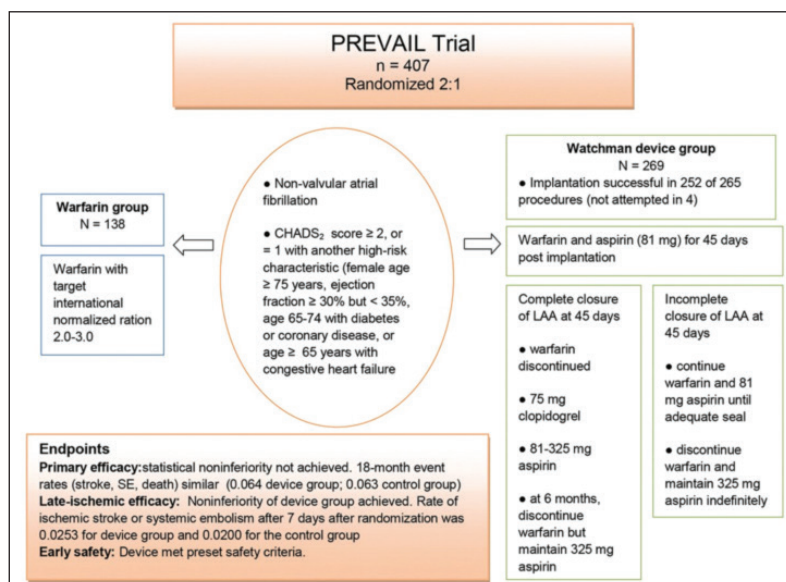
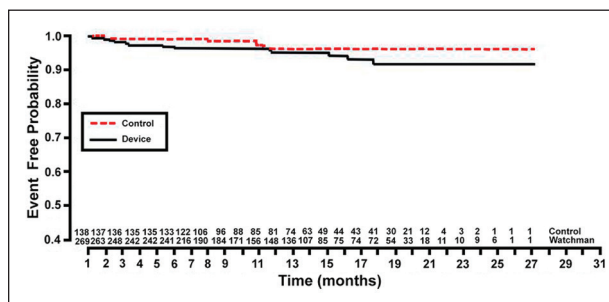


Figure 7. The PREVAIL trial provided additional information after the PROTECT AF trial.



**Figure 8.** Kaplan-Meier curve: freedom from first primary endpoint (intention-to-treat). Primary efficacy rates for Watchman (solid line) versus warfarin (dotted line) in the intention-to-treat population show similarly high 18-month event-free rates. Reprinted from *J Am Col Cardiol*, Vol. 61, Holmes DR, et al, Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation vs long-term warfarin therapy, pp. 1–12, 2014, with permission from Elsevier.<sup>19</sup>

The late-ischemic coprimary efficacy endpoint (rate of stroke or SE > 7 days of randomization) in the device group was 0.0253 compared with 0.02 in the control group, with a risk difference of 0.0053 (95% credible interval, 0.019–0.0273), achieving noninferiority (Figure 9).

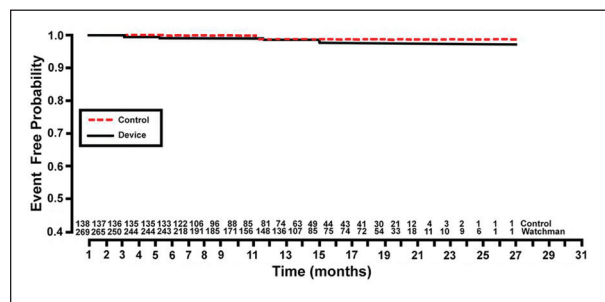
The early safety endpoint was evaluated only in the device group. The event rate was 2.2%, significantly lower than in the PROTECT AF trial. Even when all adverse events were compared, the event rate was significantly lower in the device arm of the PREVAIL trial versus the PROTECT AF trial (4.2% vs 8.7%;  $P = .04$ ). The rate of pericardial effusions needing pericardiocentesis decreased (1.5% vs 2.4%;  $P = .036$ ), and the number of participants needing surgical repair also decreased (0.4% vs 1.6%;  $P = .027$ ).

The results of the PREVAIL trial suggested that LAA occlusion was not inferior to warfarin for ischemic stroke prevention or SE > 7 days postprocedure. Noninferiority in the overall efficacy (stroke, SE, death) was not achieved, with low event rates in the device and control arms. It also showed significant improvement in procedural success and safety.

Comparative data from PROTECT AF,<sup>18</sup> CAP (Continued Assess PROTECT AF) registry,<sup>20</sup> and the PREVAIL trial<sup>19</sup> suggest significant improvement in the safety of the Watchman LAA closure device with increased operator experience (Table 1).

## COSTS AND QUALITY OF LIFE

A recent analysis of the cost utility and quality-of-life impact of LAA closure compared with warfarin for stroke prevention in AF was performed by Reddy et al using the PROTECT AF 4-year data.<sup>21</sup> They found that LAA closure was cost-effective at 6 years and less expensive and most



**Figure 9.** Kaplan-Meier curve: freedom from second primary endpoint event (intention-to-treat). Late-ischemic events (stroke or systemic embolism > 7 days after randomization) for Watchman (solid line) versus warfarin (dotted line) in the intent-to-treat population demonstrated noninferiority for the rate difference endpoint. Reprinted from *J Am Col Cardiol*, Vol. 61, Holmes DR, et al, Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation vs long-term warfarin therapy, pp. 1–12, 2014, with permission from Elsevier.<sup>19</sup>

effective at 10 years, with patients having fewer disabling strokes and a higher quality of life.

Singh et al performed an analysis from the perspective of the Ontario Ministry of Health and Long Term Care, the third-party payer for insured health services in Ontario, Canada, that found similar costs associated with OACs and LAA closure (Table 2).<sup>22</sup> They concluded that LAA closure for stroke reduction was cost-effective compared to warfarin in patients with NVAF.

The FDA recently recommended that use of the Watchman device for LAA closure should only be considered in patients with NVAF who are at an increased risk for stroke, are suitable candidates for warfarin, and have an appropriate reason to seek a nondrug alternative. It should not be used in patients with left ventricular thrombus, patients who have an allergy to nickel or titanium, or who have not had a previous device closure of atrial septal defect or patent foramen ovale. Currently, the European Society of Cardiology guidelines for AF recommend that percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term OAC (level of evidence class IIb).

## CONCLUSION

The Watchman LAA closure device is the only FDA-approved percutaneous device for LAA closure. It has been shown to be safe, efficacious, and cost-effective in stroke prevention in patients with NVAF and an increased risk of stroke. Its use involves a learning curve, and periprocedural complications significantly reduce with increasing operator experience.

**TABLE 1. COMPARISON OF OUTCOMES IN DEVICE PATIENTS IN PROTECT AF, CAP, AND PREVAIL**

|                                        | Protect AF (%) | CAP (%) | PREVAIL (%) | P Value |
|----------------------------------------|----------------|---------|-------------|---------|
| Implant success                        | 90.9           | 94.3    | 95.1        | .04     |
| All 7 days procedural complications    | 8.7            | 4.2     | 4.5         | .004    |
| Pericardial effusion requiring surgery | 1.6            | 0.2     | 0.4         | .03     |
| Pericardiocentesis                     | 2.4            | 1.2     | 1.5         | .318    |
| Procedure-related stroke               | 1.1            | 0       | 0.7         | .02     |
| Device embolization                    | 0.4            | 0.2     | 0.7         | .368    |

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**TABLE 2. AVERAGE DISCOUNTED LIFETIME COST OF STROKE PREVENTION TREATMENTS IN AF**

|               |          |
|---------------|----------|
| Warfarin      | \$21,429 |
| Dabigatran    | \$25,760 |
| LAA occlusion | \$27,003 |

Note: Analysis performed from perspective of Ontario Ministry of Health and Long Term Care, the third-party payer for insured health services in Ontario, Canada.

Future randomized, controlled trials with larger cohorts of patients and narrow, prespecified noninferiority margins would clarify the shortcomings of the current evidence base. Such trials are needed to evaluate the use of the Watchman device compared to novel oral anticoagulants (which are fast emerging as the standard of care for stroke prevention in AF), as well as to evaluate the use of the Watchman device in patients with a higher risk of stroke (CHADS<sub>2</sub> ≥ 2), in the current era of AF ablation, in valvular AF, and in patients undergoing open heart surgery.

In addition, studies are needed to determine the optimal antiplatelet regimen after LAA closure, further evaluate its long-term cost-effectiveness, and establish whether data specific to the Watchman device can be extrapolated to other LAA closure devices. Subsequent trials should also address the role of LAA morphology in risk stratification of stroke for patients with AF and the relationship between morphology and optimal device shape(s). ■

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